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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *93-105,144,145,148 and 149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *93-105, 144, 145, 148 and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 93, 144 and 148 has been amended. Claims 106-120, 146, 147, 150 and 151 have been canceled. Claims 93-105, 144, 145, 148 and 149 are pending and under consideration.

Sections of Title 35, U.S. Code not found in this action can be found in a previous Office action.

Claims 93-97, 102-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lido et al (Journal of Clinical Investigation, 1993, Vol. 92, pp. 2440-2447) or Resemble et al (Cancer Immune Immunotherapy, 1996, Vol. 42, pp. 115-121) in view of Chair et al (Cancer Research, 1992, Vol. 52, pp. 127-131).

It is noted that the recitation of "synergistic combination" implies that composition and the contents of the composition will be used to affect synergy between the two agents, and as such is an "intended use" of said composition which is not given patentable weight for determining novelty or unobviousness of a product claim.

Lidor et al teach that immunotoxin modulate the sensitivity of ovarian cancer cells to alkylators and that the toxicity produced by immunotoxins operate by a mechanism which is distinct from alkylating agents, and thus the combination is advantageous for reasons of imparting to the cancerous cells two separate toxins (page 2446, first column, lines 32-40). Lidor et al teach that the toxin portion of the immunotoxin was ricin A chain (page2440, first column, lines 11-12 under the heading of "Drugs and Immunoconjugates" and reference 9). Lidor et a do not teach the combination comprising maytansinoid as the toxic portion of the immunoconjugate.

Rosenblum et al teach that 5-FU, cisplatin, interferons alpha and gamma and etoposide augmented the cytotoxicity of an immunotoxin comprising gelonin and an anti gp-240 antibody which binds to a surface glycoprotein on melanoma cells (page 115, first column, lines 3-6, and page 120, first column, lines 7-9, figure 9 and legend for figure 9). Rosenblum et al do not teach the combination comprising maytansinoid as the toxic portion of the immunoconjugate

Chari et al teach the chemical synthesis of the structures of claims 102-105, 115-117 and 120. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen

on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction"). Chari et al teach that a method of overcoming this difficulty with anticancer drugs is to replace the current anticancer drugs with compounds which have 100 to 1000-fold higher cytotoxicity and conjugate these drugs to antibodies via a disulfide linkage which can be cleaved inside the cell to release the active drug (page 127, first column, lines 32-37 under the heading of "Introduction"). Chari et al identify maytansine as such a drug having 100 to 1000-fold higher toxicity in a range of human cancer cell lines (page 128, first column, first paragraph under "Results and Discussion"). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the ricin A chain immunoconjugate in the combination of immunotoxin and cisplatin taught by Lidor et al or to substitute maytansinoid for the gelonin of the immunoconjugate taught by Rosenblum et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al on the high therapeutic index afforded by the use of a maytansinoid immunoconjugate versus ricin A chain because the disulfide linkers provided by Chari et al for the maytansinoid immunoconjugates would be efficient at releasing the toxic maytasinoid for the antibody once internalized by the cell. One of skill in the art would expect that the maytansinoid immunotoxin would have a similar therapeutic potential as the ricin A immunotoxin of Lidor et al or of gelonin in the immunoconjugate taught by Rosenblum et al.

Claims 93-97, 99, 102-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidor et al and Chari et al or Rosenblum et al and Chari et al as applied to claims 93-97, 102-110, 115-120 above, and further in view of Schlom (Monoclonal Antibodies: They're More and Less Than

You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134, cited in s previous Office action).

Claim 99 embodies the composition of claim 93 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claim 112 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2.

The combination of Lidor et al and Chari et al or Rosenblum et al and Chari et al do not specifically teach immunotoxins wherein the antigen-binding portion is Fv, Fab, Fab' or F(ab')2.

Schlom teaches the advantages of antibody fragments such as Fab'2, Fab or Fv over the parent marine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 97, second column, line 22 to page 98, second column, line 5 and page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30).

It would have been prima facie obvious at the time the claimed invention was made to substitute the antigen-binding fragment, such as Fab'2, Fab or Fv, in place of the whole antibodies in the immunoconjugate taught by Lidor et al or Rosenblum et al. One of skill in the art would have been motivated to do so by the teachings of Schlom on the improved efficacies afforded by the administration of antibody fragments versus whole antibodies.

Claims 93-97, 99, 101-105 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidor et al and Chari et al or Rosenblum et al and Chari et al as applied to claims 93-97, 102-110, 115-120 above, and further in view of Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) and (Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134).

Claim 101 embodies the pharmaceutical composition of claim 93 wherein the monoclonal antibody or fragment thereof is humanized C242. Claim 148 is drawn to a pharmaceutical composition comprising a synergistic combination of paclitaxel and a humanized

monoclonal antibody or a fragment thereof that binds to an antigen expressed by small cell lung cancer, a non-small cell lung cancer or a colorectal cell. The combinations of Lidor et al and Chari et al or Rosenblum et al and Chari et al do not specifically teach the combination of a humanized C242-DM1 conjugate.

Liu et al teach a C242-DM1 conjugate (pages 170 to 171 in sections 2 and 3 Liu et al teach that the C242 maytansinoid conjugate killed antigen positive COLO 205 cells in vitro and caused decreased tumor burden of transplanted human colon cancer xenografs in immunodeficient mice.).

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of marine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the marine antibodies (pages 97-98, bridging paragraph).

It would have been prima facie obvious at the time the claimed invention was made to combine a humanized C242-DM1 immunotoxin with cisplatin for treatment of patients with colorectal cancer. One of skill in the art would have been motivated to do so by the teachings of Lidor et al on the general teachings regarding administering to a cancer cell two toxic moieties which differ in the means by which toxicity is induced and the further example provided by the interaction between the immunotoxin of Rosenblum et al (which is not related by antigen-binding or toxic moiety) and cisplatin. One of skill in the art would have a reasonable expectation that the combination with platinum would be at greater than either the immunotoxin or the platinum as a single agent and therefore efficacious. One of skill in the art would be motivated to make the humanized version of the C242 antibody for administration of the maytansinoid immunoconjugate to humans. One of skill in the art would also be motivated to make the scoff fragment of the C242 for administration to humans based on the teachings of Liu et al regarding the poor penetration of immunoconjugates into tumor (page 170, first column, lines 11-12) and the teachings of Schlom on the enhanced ability of scoff to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments. One of skill

in the art would logically be motivated to make a reagent which would maximize the delivery of the maytansinoid to the tumor. By making a humanized C242 antibody, the lack of a HAMA response will allow more of the antibody to reach the tumor on subsequent doses. By making a scoff from C242 the smaller fragment will have a decreased HAMA response and better ability to penetrate into the tumor.

Claims 93-98, 100-105, 144, 145, 148 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidor et al and Chari et al or Rosenblum et al and Chari et al as applied to claims 93-97, 102-110, 115-120 above, and further in view of Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190, cited in a previous Office action) and (Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134).

Claim 98 embodies the composition of claim 93 wherein the monoclonal antibody binds to a CD5 antigen. Claim 100 embodies the composition of claim 93 wherein the antibody or a fragment thereof is humanized N901.

The combinations of Lidor et al and Chari et al or Rosenblum et al and Chari et al do not specifically teach the combination of a humanized C242-DM1 conjugate.

Liu et al (AACR) teach that the administration an immunotoxin conjugate comprising the humanized N901 antibody and maytansinoid (DM1) was effective at killing human small cell lung xenographs in immunodeficient mice. The abstract of Lynch et al teaches that N901 is a monoclonal antibody that binds to the CD56 neural cell adhesion molecule of NCAM., thus fulfilling the specific embodiment of claims 98and 11 specifying binding to CD56. Liu et al do not teach the administration of cisplatin in conjunction with the immunotoxin.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of marine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the marine antibodies (pages 97-98, bridging paragraph).

It would have been prima facie obvious at the time the claimed invention was made to combine a humanized N901-DM1 immunotoxin with cisplatin for treatment of patients with small cell lung cancer. One of skill in the art would have been motivated to do so by the teachings of Lidor et al on the general mechanism affording synergy with combinations of immunotoxins and alkylating agents and the further example provided by the synergistic interaction between the immunotoxin of Rosenblum et al (which is not related by antigen-binding or toxic moiety) and cisplatin. One of skill in the art would have a reasonable expectation that the combination with platinum would be at least as effective than the administration of the immunotoxin or cisplatin as single agents.

One of skill in the art would be motivated to make the humanized version of the N901 antibody for administration of the maytansinoid immunoconjugate to humans. One of skill in the art would also be motivated to make the scoff fragment of the N901 for administration to humans based on the teachings of Liu et al regarding the poor penetration of immunoconjugates into tumor (page 170, first column, lines 11-12) and the teachings of Schlom on the enhanced ability of scoff to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments. One of skill in the art would logically be motivated to make a reagent which would maximize the delivery of the maytansinoid to the tumor. By making a humanized N901 antibody, the lack of a HAMA response will allow more of the antibody to reach the tumor on subsequent doses. By making a scoff from N901 the smaller fragment will have a decreased HAMA response and better ability to penetrate into the tumor.

The rejection of claims 93-97, 99, 102-105, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020 in view of Lidor et al is maintained for reasons of record.

Claims 1-6 of the '020 patent are drawn in part to cytotoxic agents comprising one or more maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens. Claims 7-12 are drawn to pharmaceutical composition comprising maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal

antibody or fragment thereof is selective for tumor cell antigens. Conjugation of the monoclonal antibody to the maytansinoid via the C3 position of maytansinoid is the same as the structures of instant claims 102,-105 and 115-117.

Lidor et al teach that immunotoxin modulate the sensitivity of ovarian cancer cells to alkylators and that the toxicity produced by immunotoxins operate by a mechanism which is distinct from alkylating agents, and thus the combination is advantageous for reasons of imparting to the cancerous cells two separate toxins (page 2446, first column, lines 32-40). Lidor et al teach that the toxin portion of the immunotoxin was ricin A chain (page2440, first column, lines 11-12 under the heading of "Drugs and Immunoconjugates" and reference 9). It would have been prima facie obvious to include cisplatin with the pharmaceutical compositions of claims 7-12. One of skill in the art would have been motivated to do so by the teachings of Lidor et al on the desirability of administering to a cancer cell two different toxic agents which exert toxicity in the cell by differing mechanisms.

Claims 93-97, 99, 102-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegall et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A185) in view of Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131).

Siegall et al teach that combination therapy with BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to have greater anti-tumor effects in rodents carrying large tumor burdens than either agent alone. The immunotoxin of Siegall et al comprised a single chain antibody which binds to the LeY antigen expressed by human carcinomas, thus fulfilling the specific embodiment of an antibody or fragment thereof that binds to an antigen expressed by a cancer cell, and the specific embodiment of a fragment of a monoclonal antibody that is Fv. Siegall et al teach an immunotoxin conjugated to PE40, which is a modified from of pseudomonas endotoxin . Siegall et al do not teach a BR96 sVf-maytansinoid.

Chari et al teach the chemical synthesis of the structures of claims 102-105, 115-117 and 120. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell

lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the PE40 toxin in the combination of BR96-sFv-PE40 taught by Siegall et all. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al on the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity. It is noted that the recitation of "synergistic combination" in the instant claims implies that composition will be used to affect synergy between the two agents, and as such is an "intended use" of said composition which is not given patentable weight for determining novelty or unobviousness of a product claim.

Claims 93-97, 99, 101-105, , 144, 146 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) in view of Watson et al (Proc Ammu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A2997) and (Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134).

Liu et al teach a C242-DM1 conjugate (pages 170 to 171 in sections 2 and 3 Liu et al teach that the C242 maytansinoid conjugate killed antigen positive COLO 205 cells in vitro and caused decreased tumor burden of transplanted human colon cancer xenographs in immunodeficient mice.). Liu et al teach that a reason for lack of clinical efficacy with antibody drug conjugates can be attributed to insufficient accumulation of drug both intratumorally and intracellularly to kill large numbers of tumor cells (page 169, second column, last paragraph). Liu et al teach that this phenomenon can be attributed to the limited expression of target antigens on tumor cells which restricts the amount of drug delivered (page 170, first column, line 8-10) as well as lack of cytotoxic potency and inefficient release of the active drug from the antibody inside the cell (page 170, first column, lines 2-7 and lines 14-15). Liu et al teach that maytansinoids effect cell killing by interfering with the formation of microtubules and

depolymerization of already existing microtubules (page 170, column 1, lines 23-26). Liu et al do not teach the administration of the C242-Dm1 conjugate with taxol.

Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of marine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the marine antibodies (pages 97-98, bridging paragraph). Schlom teaches the advantages of single chain antibodies over the parent marine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). One of skill in the art would be motivated to make the humanized version of the C242 antibody for administration of the maytansinoid immunoconjugate to humans. One of skill in the art would also be motivated to make the scoff fragment of the C242 for administration to humans based on the teachings of Liu et al regarding the poor penetration of immunoconjugates into tumor (page 170, first column, lines 11-12) and the teachings of Schlom on the enhanced ability of scoff to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments. One of skill in the art would logically be motivated to make a reagent which would maximize the delivery of the maytansinoid to the tumor. By making a humanized C242 antibody, the lack of a HAMA response will allow more of the antibody to reach the tumor on subsequent doses. By making a scoff from C242 the smaller fragment will have a decreased HAMA response and better ability to penetrate into the tumor.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized C242-DM1

immunoconjugate with taxol or the administration of scoff of C242-DM1 with taxol for the treatment of colorectal tumors. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al on the limited expression of target antigens on tumor cells which restricts the amount of drug delivered as an impediment to the clinical efficacy of immunoconjugates and the teachings of Liu et al on the antitubulin mode of action of maytansinoid, the delivered drug. One of skill in the art would realize that tumors which are lacking the CanAg to which the C242 antibody binds will not internalize the immunoconjugate and thus will not be exposed to enough anti-tubulin inhibiting drug within the cytoplasm. One of skill in the art would understand that for such tumor cells the administration of the immunotoxin in combination wit taxol would compensate for the lack of delivered drug to cells which are lacking the CaAg. One of skill in the art would be motivated to combine the C242-DM1 immunotoxin with taxol in order to exert a cytotoxic effect on cells which do not express enough of the CanAg targeted by the C242 antibody to result in accumulation of a sufficient amount of the maytansinoid to be cytotoxic. It is noted that the recitation of "synergistic combination" in claims 105 and 120 implies that composition and the contents of the kit will be used to affect synergy between the two agents, and as such is an "intended use" of said kit or composition which is not given patentable weight for determining novelty or unobviousness of a product claim.

Claims 93-97, 99, 101-105, 144, 145, 148 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu, Watson et al and Schlom as applied to claims 93-97, 99, 101-110, 112, 114-119, 144, 146, 148 and 150 above, and in further view of Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131).

Chari et al teach the chemical synthesis of the structures of claims 102-105. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9).

It would have been prima facie obvious to use maytansinoid as the toxic portion of an immunoconjugate in combination with a chemotherapeutic agent. One of skill in the art would have been motivated to do so by the teachings of Chari et al on the high specific activity of the immunoconjugate coupled with low systemic toxicity.

Claims 93-98, 100-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al (Clinical Oncology, 1994, Vol. 6, pp. 40-48) in view of Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and the abstract of Lynch et al (Journal of Clinical oncology, 1997, Vol. 15, pp. 723-734) and Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action).

Claim 98 embodies the composition of claim 93 wherein the monoclonal antibody binds to a CD5 antigen. Claim 100 embodies the composition of claim 93 wherein the antibody or a fragment thereof is humanized N901.

The abstract of Guchelar et al teaches that taxol shows a 37% response rate in the treatment of advanced small cell lung cancer. The abstract does not teach the administration of the humanized N901-DM1 conjugate.

Liu et al (AACR) teach that the administration an immunotoxin conjugate comprising the humanized N901 antibody and maytansinoid (DM1) was effective at killing human small cell lung xenographs in immunodeficient mice. The abstract of Lynch et al teaches that N901 is a monoclonal antibody that binds to the CD56 neural cell adhesion molecule of NCAM., thus fulfilling the specific embodiment of claims 98 and 11 specifying binding to CD56. Liu et al do not teach the administration of taxol

The abstract of Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.
Liu et al(EOID) teach that maytansinoids kill cells by interfering with the formation of microtubules and depolymerization of already existing microtubules (page 170, first column, lines 2326). Liu et al teach the modified structure of maytansinoid allowing for the attachment of a monoclonal antibody by means of the thiol "handle" (figure1, structure 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized N901-DM1 immunoconjugate with taxol for the treatment of small cell lung carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Guchelaar et al who indicate that the administration of taxol alone has some efficacy in the treatment of advanced small cell lung carcinoma; the teachings of Liu et al (AACR) on the efficacy of the N901-DM1 immunoconjugate against human small cell lung cancer xenographs and the teachings of the abstract of Iwasaki et al and Liu (EOID) on the different binding sites of maytansinoid and taxol on tubulin, and the teachings of Liu (EOID) and the abstract of Watson on the effects exerted on tubulin by taxol and maytansinoid . One of skill in the art would reasonably conclude that the efficacy of the combination of the immunotoxin and the drug would be greater than for either the immunotoxin as a single agent or the drug as a single agent. It is noted that the recitation of "synergistic combination" in the claims implies that composition will be used to affect synergy between the two agents, and as such is an "intended use" of said composition which is not given patentable weight for determining novelty or unobviousness of a product claim.

Claims 93-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al Clinical Oncology, 1994, Vol. 6, pp. 40-48) and Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and Liu (Expert opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172 as applied to claims 93-98, 100-111, 113, 115-120 above, and further in view of Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134).

Claim 93 is drawn in part to a synergistic combination with a maytansinoid compound linked to fragments of a monoclonal antibody. Neither of Guchelaar et al, Liu et al (AACR), or Liu et al (EOID), teach the administration of fragments of N901.

Liu et al (EOID) teach that a lack of clinical efficacy of immunoconjugates can be attributed to poor penetration of said immunoconjugates into tumors (page 170, first column, lines 11-12).

Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, and increased penetration into tumor masses, (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine taxol with scoff conjugated to DM1 in place of N901-DM1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al regarding the lack of tumor penetration as a reasons for reduced toxicity of immunoconjugates in vivo, and the teachings of Schlom et al regarding the administration of scoff in place of whole antibodies for increasing tumor penetration in vivo.

Applicant argues that the unexpected property of providing a synergistic effect must be taken into consideration.
Applicant has provided a Declaration under 1.131 asserting the synergistic properties of compounds in the claimed compositions. This has been considered but not found persuasive. The examiner is not questioning the fact that the combination is synergistic.
It is further noted that the M.P.E.P (2144). teaches that
The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972)

Thus, there is strong motivation to make the composition combining the two prior art agents to attain an additive effect.

Applicant has provided excerpts from In re Papesch, and In re McLamore 154, USPQ 114 (CCPA 1967) to argue for unexpected properties of a composition. this has been considered but

not found persuasive. None of the examples address the unobviousness of a composition which was a combination of two known agents recognized by the art to be useful for the same purpose for killing tumor cells. None of the examples provided give information as to a specific claim requiring "synergism" as an intended use for a product.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
8/6/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER